DETAILED ACTION

Status of the Application

This Office Action is in response to applicant's arguments filed on 9/30/09. Claim(s) 13-16, 20-21 have been cancelled. Claim(s) 1-12, 17-19, 22-25 are pending. Claim(s) 19, 23-24 have been withdrawn. Claim(s) 1-12, 17-18, 22, 25 are examined herein.

Applicant's arguments have been fully considered but found not persuasive. The rejection(s) of the last Office Action are maintained for reasons of record and repeated below for Applicant's convenience.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham vs John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-12, 22, 25 are rejected under 35 U.S.C. 103(a) as being obvious over Dietrich et al. ("Oxcarbazepine in Affective and Schizoaffective Disorders" *Pharmacopsychiatry*, 2001, 34, 242-250) in view of Almeida et al. ("Safety, Tolerability and Pharmacokinetic Profile of BIA-2-093, a Novel Putative Antiepileptic Agent, during First Administration to Humans," Drugs R&D 4(5): pp. 269-284, 2003).

The instant claims are directed to a method of treating manic episodes of bipolar disorder in a patient in need thereof by administering eslicarbazepine acetate.

Dietrich et al. teaches that oxycarbamazepine as well as carbamazepine are effective in the treatment of acute mania and rapid cycling in patients with bipolar affective disorders (pg. 242, right column, Table 1, and conclusion). Concurrent drug treatments with mood-stabilizers and antidepressants are not uncommon in affective disorders (pg. 245, right column, paragraph 2). Dietrich et al. also teach that since oxycarbamazepine does not interact with the cytochrome P450-enzyme system, co-administration with antidepressants might be well-tolerated in affective and schizoaffective disorders (sentence bridging pgs. 247-248). Table 1 shows various dosages of oxycarbamazepine ranging from 500 mg to 2.1 grams per day.

However, Dietrich et al. fail to specifically disclose eslicarbazepine acetate.

Almeida et al. teach that no clinically significant abnormalities in laboratory safety tests, vital signs, weight, physical examination or ECG with BIA 2-093 (also known as eslicarbazepine acetate), therefore considered to be safe and well-tolerated for human administration (abstract). BIA 2-093 is derived from carbamazepine and oxcarbazepine since the dibenzazepine nucleus bearing the 5-carboxamide is shared, while structurally

different at the 10, 11-position. This molecular variation results in differences in metabolism, namely by preventing the formation of toxic epoxide metabolites and unnecessary production of enantiomers or diastereoisomers of metabolites and conjugates without losing antiepileptic potency (pg. 270, left column, second paragraph and Figure 1).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to have substituted eslicarbazepine acetate as taught by Almeida et al, for oxycarbamazepine in the method of treating manic episodes of bipolar disorder as taught by Dietrich et al.

A person of ordinary skill in the art would have been motivated to have substituted eslicarbazepine acetate as taught by Almeida et al, for oxycarbamazepine in the method of treating manic episodes of bipolar disorder as taught by Dietrich et al. because: (1) eslicarbazepine acetate is a derivative of oxycarbamazepine; (2) the functional equivalency of sharing a common structural core; (3) the added benefit of preventing the formation of toxic epoxide metabolites and unnecessary production of enantiomers or diastereoisomers of metabolites and conjugates; and (4) because eslicarbazepine acetate is safe and well-tolerated for human administration. Therefore, one of ordinary skill in the art would have had a reasonable expectation of success in treating manic episodes of bipolar disorder in a patient in need thereof by administering eslicarbazepine acetate in the claimed dosage range.

Claim(s) 17-18 are rejected under 35 U.S.C. 103(a) as being obvious over Dietrich et al. ("Oxcarbazepine in Affective and Schizoaffective Disorders"

Pharmacopsychiatry, 2001, 34, 242-250) and Almeida et al. ("Safety, Tolerability and Pharmacokinetic Profile of BIA-2-093, a Novel Putative Antiepileptic Agent, during First Administration to Humans," Drugs R&D 4(5): pp. 269-284, 2003) as applied to claims 1-12, 22, 25 in view of Beasley et al. (US Patent 5,605,897).

The instant claims are directed to a method of treating manic episodes of bipolar disorder in a patient in need thereof by administering eslicarbazepine acetate and olanzapine.

Dietrich and Almeida et al. teach as discussed above, however, fail to disclose olanzapine.

Beasley et al. teach the olanzapine is useful in the treatment of bipolar disorder.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to have combined olanzapine as taught by Beasley et al. with eslicarbazepine acetate in the method of treating manic episodes of bipolar disorder as taught by Dietrich and Almeida et al.

A person of ordinary skill in the art would have been motivated to combine olanzapine as taught by Beasley et al. with eslicarbazepine acetate in the method of treating manic episodes of bipolar disorder as taught by Dietrich and Almeida et al. because both olanzapine and eslicarbazepine acetate are useful for treating bipolar disorder.

"It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... The idea of combining them flows logically from their

having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Response to Arguments

Applicant argues that the compounds used in the present invention are surprisingly useful for the treatment of affective disorders, in particular bipolar disorder.

Regarding the establishment of unexpected results or synergism, a few notable principles are well settled. The Applicant has the initial burden to explain any proffered data and establish how any results therein should be taken to be unexpected and significant. See MPEP 716.02 (b). It is applicant's burden to present clear and convincing factual evidence of nonobviousness or unexpected results, i.e., side-by-side comparison with the closest prior art in support of nonobviousness for the instant claimed invention over the prior art. The claims must be commensurate in the scope with any evidence of unexpected results. See MPEP 716.02 (d). With regard to synergism, a prima facie case of synergism has not been established if the data or result is not obvious. The synergism should be sufficient to overcome the obviousness, but must also be commensurate with the scope of the claims. Further, if the Applicant provides a DECLARATION UNDER 37 CFR 1.132, it must compare the claimed subject matter with the closest prior art in order to be effective to rebut a prima facie case if obviousness. See MPEP 716.02 (e).

Applicant argues that there is no specific teaching in Dietrich that oxcarbazepine is useful in treating bipolar disorder. Dietrich states that no valid conclusions can be drawn about the prophylactic effects of oxycarbazepine in bipolar patients.

This is not persuasive because the Dietrich reference clearly encompasses the claimed patient population. For example, bipolar affective disorders are taught on page 242, right column in addition to Table 1 and the conclusion. Further, carbamazepine is clearly taught to be effective in the treatment of classical bipolar disorder, acute mania, and other major affective disorders. Table 1 shows oxycarbazepine in the treatment of this patient population. The conclusion reiterates that oxycarbazepine is effective in the treatment of acute mania and other affective disorders.

Applicant argues against the Almeida reference in that simply because a compound is a derivative of another compound and appears to be safe to administer to humans is not a sufficient basis for combining references.

This is not persuasive because carbamazepine, oxcarbazepine, and eslicarbazepine acetate all share a common structural core consisting of a dibenzazepine nucleus bearing a 5-carboxamide. Since a prima facie case of obviousness has been established, it is Applicant's burden to show that eslicarbazepine acetate would not behave in the same manner as carbamazepine or oxcarbazepine.

Applicant argues that there is no experimental data in Beasley, either preclinical or clinical, that demonstrate that olanzapine is in fact useful in the treatment of bipolar disorders or to select bipolar disorder from the numerous diseases, conditions, and conditions that Beasley alleges can be treated with olanzapine.

This is not persuasive because in the Beasley patent, claim 1 is drawn to treating a handful of diseases, including bipolar disorder by administering olanzapine.

A patent shall be presumed valid. Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims; dependent or multiple dependent claims shall be presumed valid even though dependent upon an invalid claim. The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity. *35 U.S.C. 282 Presumption of Validity*

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong S. Chong whose telephone number is (571)-272-8513. The examiner can normally be reached on M-F, 9-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SREENI PADMANABHAN can be reached on (571)-272-0629. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Yong S. Chong/
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YSC